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Use of Environmental Tobacco Smoke Constituents as Markers for Exposure

Judy S. LaKind,[1] Roger A. Jenkins,[2] Daniel Q. Naiman,[3] Michael E. Ginevan,[4] Carol G. Graves,[5,6] and Robert G. Tardiff[5]

The 16-City Study analyzed for gas-phase environmental tobacco smoke (ETS) constituents (nicotine, 3-ethenyl pyridine [3-EP], and myosmine) and for particulate-phase constituents (respirable particulate matter [RSP], ultraviolet-absorbing particulate matter [UVPM], fluorescing particulate matter [FPM], scopoletin, and solanesol). In this second of three articles, we discuss the merits of each constituent as a marker for ETS and report pair-wise comparisons of the markers. Neither nicotine nor UVPM were good predictors for RSP. However, nicotine and UVPM were good qualitative predictors of each other. Nicotine was correlated with other gas-phase constituents. Comparisons between UVPM and other particulate-phase constituents were performed. Its relation with FPM was excellent, with UVPM approximately 1½ times FPM. The correlation between UVPM and solanesol was good, but the relationship between the two was not linear. The relation between UVPM and scopoletin was not good, largely because of noise in the scopoletin measures around its limit of detection. We considered the relation between nicotine and saliva cotinine, a metabolite of nicotine. The two were highly correlated on the group level. That is, for each cell (smoking home and work, smoking home but nonsmoking work, and so forth), there was high correlation between average cotinine and 24-hour time-weighted average (TWA) nicotine concentrations. However, on the individual level, the correlations, although significant, were not biologically meaningful. A consideration of cotinine and nicotine or 3-EP on a subset of the study whose only exposure to ETS was exclusively at work or exclusively at home showed that home exposure was a more important source of ETS than work exposure.

KEY WORDS: 16-City Study; environmental tobacco smoke; markers; nicotine; personal monitoring; saliva cotinine; workplace exposure.

1. INTRODUCTION

A fundamental aspect of data collection in environmental tobacco smoke (ETS) research involves the selection of chemicals for inclusion in the sampling and analysis. According to the guidelines set forth by the National Research Council (NRC),[1] any chemical selected for use as an ETS marker should be present in a fairly consistent ratio to the ETS component(s) of interest under a range of environmental conditions. Generally, researchers have focused on either or both of two criteria for ETS chemical selection: first, how well the chemical performs as a marker for ETS, and second, whether the chemical is present at sufficiently high air concentrations to be measurable. An additional consideration has been whether the ETS-related chemical has toxicological/pharmacological properties of interest

[1] LaKind Associates, LLC.
[2] Oak Ridge National Laboratory.
[3] The Johns Hopkins University, Department of Mathematical Sciences.
[4] M. E. Ginevan and Associates.
[5] The Sapphire Group, Inc., 3 Bethesda Metro Center, Suite 700, Bethesda, MD 20814.
[6] To whom all correspondence should be addressed.

(i.e., whether the chemical causes adverse health effects).

The ETS-related chemicals analyzed for in the 16-City Study[2,3] included the gas-phase chemicals (nicotine, myosmine, and 3-ethenyl pyridine [3-EP]) and the particulate-phase constituents (respirable particulate matter* [RSP], ultraviolet-absorbing particulate matter [UVPM], fluorescing particulate matter [FPM], solanesol, and scopoletin).

The study also analyzed saliva samples for cotinine, a metabolite of nicotine. Each of these chemicals meets at least two of the preceding criteria. That is, each has been explored in previous research as a potential marker for ETS,[4-8] and each has been determined as present in sufficient quantities to be measurable in field or chamber studies.

It should be noted that these chemicals were not necessarily selected because of their toxicological impacts. However, both nicotine and ETS-related particulate phases have been the subject of toxicological/pharmacological studies (see, for example, Benowitz[9] and Benowitz and Jacob[10]). Also of note, most ETS-related chemicals of toxicological interest are not present in the work or home environment in sufficient quantities to be measurable with current sampling capabilities.

This article examines relationships among the ETS markers analyzed in the 16-City Study and discussed in the first article in this series of three. In the final article in this series, doses are modeled for the constituents determined in this article to be good markers for ETS.

2. REVIEW OF THE LITERATURE ON ETS-RELATED CHEMICALS AS MARKERS

Nicotine has been used extensively as a marker for estimating exposure to ETS. Several of nicotine's properties make it ideally suited for such a purpose. These include its uniqueness to tobacco smoke, its abundance in side-stream smoke,[7,11] its relative ease of measurement,[12] and the ability to sample one of its metabolites (cotinine) in several body fluids. A constant relationship between nicotine and RSP, based on time-averaged measurements, has been reported. Ratios of RSP to nicotine include, for example, 14.1 ± 1.9 : 1 in a chamber study,[12] 9 : 1 in public facilities and offices,[13] and 10.3 : 1.[14]

In contrast, the utility of nicotine as a marker of exposure to other ETS-related compounds has been challenged, principally because of its distinctly different decay kinetics. Nicotine does not exhibit first-order decay properties. Reasor[15] noted that despite the fact that nicotine is specific to tobacco smoke, nicotine should not be employed as a surrogate for other substances in ETS because nicotine ages differently from other substances and therefore correlates poorly with other ETS-related chemicals.[11,16-19]

Because of nicotine's complex decay kinetics, researchers have searched for alternative gas-phase compounds to use as markers for ETS exposure. Both myosmine and 3-EP have been suggested as candidates. Myosmine is present at 2% to 7% of the gas-phase nicotine concentration, is easily measured, is unique to ETS, and may be a conservative gas-phase tracer of ETS.[7] Results of Benner *et al.*[8] also suggest that myosmine could be used as a particulate tracer of ETS, despite the fact that it is present at low concentrations in ETS and reactive in the presence of ultraviolet (UV) radiation.

The compound 3-EP is formed by the pyrolysis of nicotine when tobacco is burned,[20] is unique to tobacco smoke, is present only in the gas phase, is similar to nicotine in concentration, and exhibits greater stability under UV irradiation than nicotine.[7] Although the use of 3-EP as an ETS marker has been criticized due to lack of correlation with source strength and detection limits,[21] the ETS concentrations of 3-EP are only slightly lower than those of nicotine, and 3-EP detection limits are 2 to 4 times lower than those for nicotine. Furthermore, 3-EP may be more suitable than nicotine as a tracer for ETS because (1) it has been shown to follow first-order decay kinetics, (2) it increases linearly with the number of cigarettes smoked, and (3) it closely tracks the vapor phase of ETS as measured by carbon monoxide.[16] Nelson *et al.*[20] reported that 3-EP followed first-order decay kinetics for the first 2 to 3 hours after smoking. Its decay then slowed, suggesting that an adsorption/desorption phenomenon similar to, but not as pronounced as, that observed for nicotine was taking place. Nelson *et al.*[20] concluded that 3-EP is a good predictor of gas-phase ETS components. Balter *et al.*[18] also found 3-EP to be a conservative tracer for the particulate portion of ETS.

Respirable particulate matter commonly has been used as a marker for ETS exposure because (1) compounds of toxicological significance are found in the particulate phase ETS, (2) RSP has been correlated with the number of cigarettes observed in in-

*RSP is defined as particles 3.5 μm or smaller.

door environments, and (3) RSP is easily measurable.[5] However, because RSP is not unique to ETS, it is likely that total RSP levels represent an overestimate, to a variable and in most cases an unknown degree, of exposure to ETS-related RSP.[22,23] Therefore, fractions of RSP that can be related to combustion are thought to be more representative of exposure to ETS, although it is likely that these too represent a possible overestimation, because other sources of combustion-derived RSP may be present as a result of cooking and heating or automobile and truck exhaust.

Two alternative particulate matter candidates related to combustion that have been explored to varying degrees are UVPM and FPM. Whereas UVPM is calculated by measuring ultraviolet absorption of a methanol extract of collected particulate matter,[7] FPM is based on the fluorescence of methanol extract of filters used to obtain gravimetric RSP determinations.[20] Nelson *et al.*[19] measured ETS components in a chamber over time and found that ratios between RSP and UVPM remained essentially constant.

In a later study, *Nelson et al.*[20] noted that UVPM and FPM were not unique to ETS-related particles, but that they place "an upper limit on the fraction of RSP caused by smoking." For example, in a study conducted in the home of a nonsmoker, UVPM concentrations were found to be approximately one order of magnitude lower than RSP. It was postulated that measurable UVPM most likely originated from cars, suggesting that UVPM may slightly overestimate ETS-related RSP.[22] Nelson *et al.*[20] noted that the ratio of UVPM to RSP varied by a maximum of about 60%. Ogden and Maiolo[24] hypothesized that when ETS particulate matter is the only source of RSP (e.g., in a chamber), the results for UVPM and RSP should agree. Their research demonstrated excellent agreement with UVPM/RSP ratios of approximately 1. Ogden and Maiolo[24] concluded that the ability of UVPM to predict the correct apportionment of ETS particulate matter in RSP is good. The other particulate matter, combustion-related constituent, FPM, is theoretically more specific for ETS than UVPM because of the inherent selectivity of fluorescence over UV absorbance.[20]

Two additional ETS-related chemicals, scopoletin and solanesol, have been explored as potential markers for ETS exposure. Scopoletin is a coumarin derivative found in a variety of plants, including tobacco and oak leaves,[25] cassava,[26] and seeds of two *Leguminosae* plants.[27] Because scopoletin is strongly fluorescing,[25] it has been used as a calibration surrogate for analysis of FPM.[5] Only recently has scopoletin been explored for its suitability as a marker for ETS.[5,6,25] Ogden *et al.*[6] reported results from a chamber study demonstrating that scopoletin slightly overestimated the particulate phase of ETS as measured by RSP.

Solanesol, a trisesquiterpenoid alcohol found in tobacco leaf, cigarette smoke condensate, and the RSP of ETS,[4] is unique to ETS.[8] Solanesol is the particulate component of greatest abundance in ETS, averaging about 2% to 4% of the weight of RSP collected from the ETS generated from reference cigarettes.[4,23,24] Because of its high molecular weight (631 g/mol), solanesol has very low volatility and is expected to remain part of the particulate matter even at high dilutions.[4] Therefore, solanesol is not expected to shift equilibrium between vapor and particle phases of the ETS aerosol under any normal conditions encountered in an indoor environment,[24] nor will it be lost from filter pads used for collection because of evaporation, as can happen with nicotine and other major tobacco smoke constituents.[24] Solanesol in ETS particulate matter was found to be reactive in the presence of intense ultraviolet (UV) light. However, this is not anticipated to be a factor in indoor environments.[23]

Whereas solanesol may be ETS-specific and, therefore, could serve as a useful ETS particulate matter marker,[4,18] its relationship to other constituents of ETS has not yet been clearly established.[4] Nelson *et al.*[20] found solanesol to be superior over nicotine as a marker for ETS-related RSP. We found the greatest variation in the RSP/solanesol ratio to be approximately 50%. Tang *et al.*[23] found the ratio of solanesol to other constituents of ETS to be independent of the total number of cigarettes burned. However, Ogden and Maiolo[24] reported measurable differences in the solanesol percentage of RSP delivered to the environment from different smoking products. It has been suggested that these differences might limit the usefulness of solanesol as a marker for ETS.[28] In a later study, Ogden *et al.*[6] found that solanesol concentrations, as measured in a chamber study, grouped tightly around RSP concentrations.

The average amount of solanesol in ETS inferred from data for indoor samples in the presence of heavy smoking has been reported to be 1.7 ± 0.1 wt% solanesol.[23] This is in good agreement with the value of 1.6–3.6 wt% solanesol in indoor ETS reported by Ogden and Maiolo,[24] who concluded that "[t]he ability of the UV-PM procedure to predict the

correct apportionment of ETS-PM in RSP for these conditions is quite good, while that of solanesol is excellent." According to Tang *et al.*,[23] the concentration of solanesol parallels that of particulate-phase nicotine and 3-EP in indoor environments. McAughey *et al.*[29] found solanesol levels to be approximately 1.3% of total particulate levels (measured as UVPM).

3. USE OF SELECTED ETS CHEMICALS AS MARKERS

Workplace data from cells 1 and 3 of the 16-City Study[23] were used to explore whether one chemical or group of chemicals was suitable to use as a marker for exposure to other ETS chemicals. That is, we assessed the extent to which one of the ETS constituents could be used as a *surrogate* for another constituent using personal monitoring of ETS data from study participants who worked in places that permitted smoking.

If an ETS constituent X is a surrogate for another constituent Y, then knowing the value of X leads to a prediction of the value of Y with a reasonable degree of accuracy (Y = f(X) + error, where f is some function and the error is small[8]). The ideal function has a simple form that provides a good fit to the data. If a linear relationship could be found such that Y = cX, where c is a constant, then the variable Y could be viewed as essentially a multiple of X. We used a regression approach to determine if a relationship of this form was present.

Because the distributions of the ETS constituent concentrations are much closer to log normal than normal,[9] models relating the $\log_{10}$ transformed concentrations were used.[10] We looked for the best fitting linear model relating the log-transformed concentration of X to the log-transformed concentration of Y in the form given in Eq. 1:

$$\log_{10}(Y) = \alpha + \beta \log_{10}(X), \quad (1)$$

[7] The error term is understood but not explicitly stated in the following equations.

[9] See the third article in this series.

[10] In all of the analyses in this section, $\log_{10}$ concentrations were adjusted for city because there were city differences between cells. See the first article in this series. To adjust for city, the mean $\log_{10}$ concentration of a constituent was calculated for each city and subtracted from each observation in that city. The overall mean for all cities was then added so that all cities had mean concentrations for each ETS-related constituent equal to the overall constituent mean.

where α is the intercept term, and β is the slope of the regression line. In terms of the untransformed concentrations, this relationship takes the following form:

$$Y = 10^{\alpha} X^{\beta} \quad (2)$$

(i.e., the linear relation between logarithms of the concentrations results in an exponential relation between the untransformed concentrations). Standard regression methods were used to determine if the linear model in Eq. 1 could be improved by allowing a nonlinear relationship between the log-transformed variables as in Eq. 3:

$$\log_{10}(Y) = \alpha + \beta \log_{10}(X) + \xi(\log_{10}[X])^2. \quad (3)$$

This decision was approached on an *ad hoc* basis by testing whether the quadratic model provided a significantly better fit to the data. The nonlinear model has no physical interpretation (i.e., untransforming the results gives no intuitive form).

In each case (i.e., for each pair of ETS constituents modeled), the following steps were performed. The regression model was fitted, and the values of R^2 and σ were inspected. The null hypothesis of linearity was tested against the alternative of nonlinearity. When a quadratic term was found to belong in the model, we compared the linear and the quadratic models to decide whether there was any practical difference between the two. This was done by looking for a substantial difference in the estimates of R^2 and σ between the linear and quadratic fits and by visually inspecting a plot of the pairs ($\log_{10}[X]$, $\log_{10}[Y]$) with the best-fit line and best-fit quadratic superimposed to see if there was any practical difference between the linear and quadratic fits.

For cases in which the linear model in Eq. 1 provided a good fit, and in which β was close to 1, Y was a fixed multiple of X (i.e., the fit was essentially linear for the untransformed as well as the transformed concentrations). In such cases, Eq. 2 simplifies and is equivalent to

$$Y = 10^{\alpha} X. \quad (4)$$

In Eq. 4, the ratio Y/X can be viewed as approximately a constant (i.e., 10^{α}). For certain of the ETS constituent relationships, the coefficient β was somewhat close to but not equal to 1. In such cases, it was useful to be able to conclude that β was sufficiently close to 1 so that the model with $\beta = 1$ remained practical, with the result that Y was a fixed multiple of X. In these cases, the effect of making this simplifying assumption was summarized by determining the ratio

of the two fitted values $10^{\alpha}X^{\beta}$ and $10^{\alpha}X$ for *typical* values of X.

The most interesting pairwise analyses are discussed in the following sections, including the correlations between nicotine and UVPM, between nicotine and other gas-phase compounds, and between UVPM and other particulate-phase constituents.

3.1. Nicotine/UVPM

The best fitting linear model of the transformed concentrations estimating $\log_{10}$(nicotine) given $\log_{10}$(UVPM) took the form of Eq. 1. The regression parameters α, β, σ, and R^2 are shown in Table I. The value of R^2 (.63) implies a moderately good fit. Because β is reasonably close to 1, it can be concluded that, given the UVPM concentration, the nicotine concentration is approximately $10^{-1.03}$ or 9% of the UVPM concentration.

Next, we assessed the effect of replacing β = 0.92 by 1 in the preceding analysis. In the nonlinear equation relating the untransformed nicotine concentration to the untransformed UVPM concentration (Eq. 2), X^{β} or $UVPM^{\beta}$ is replaced by UVPM (because we assumed β = 1 as in Eq. 4). The ratio $UVPM^{\beta}$/UVPM = $UVPM^{\beta-1}$ shows the relation between the nonlinear and linear models of the untransformed concentration values. This ratio was calculated for typical values of UVPM as follows:

1st quartile of UVPM (adjusted for city) = .183
ratio = 1.15

median (2nd quartile) of UVPM (adjusted for city) = .608
ratio = 1.04

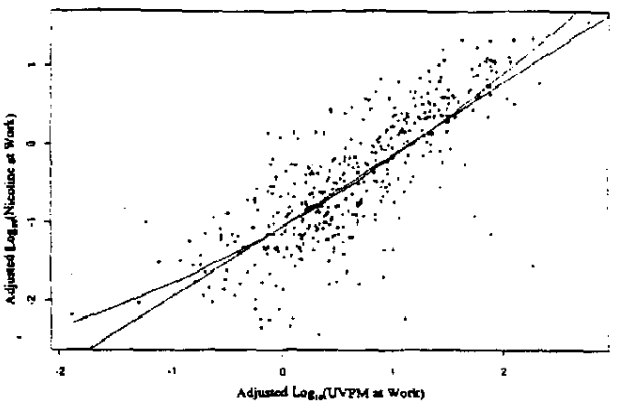

Fig. 1. Scatter plot of $\log_{10}$(nicotine at work) and $\log_{10}$(UVPM at work) (both adjusted for city) with linear and quadratic models relating the log transformed concentrations.

3rd quartile of UVPM (adjusted for city) = 1.196
ratio = .99

The effect of the simplifying assumption of replacing β by 1 is to change the nicotine prediction by no more than 16% for the range of UVPM values between the 1st and 3rd UVPM quartiles.

A plot of the fitted relationships is given in Fig. 1. A small but statistically significant quadratic term was found. However, this model provides only a slightly better fit than the linear model of the transformed concentrations. In fact, as illustrated in Fig. 1, for the values of UVPM in the center of the UVPM distribution, the fitted quadratic curve does not differ substantially from the fitted line. We conclude that the linear model tends to underpredict nicotine at the low and high ends of UVPM and very slightly to overpredict in the intermediate range of UVPM.

Table I. Regression Parameters for the Linear Model of the Transformed Concentrations Relating Y = $\log_{10}$(constituent concentration at work, adjusted for city) to X = $\log_{10}$(second constituent concentration at work, adjusted for city)

ETS constituents	α	β	σ	R^2
Nicotine/UVPM	−1.03 ± .07	.92 ± .07	.510	.63
Nicotine/RSP	−1.58 ± .22	.83 ± .15	.727	.25
Nicotine/3-EP	.27 ± .04	1.07 ± .04	.335	.83
Nicotine/Myosmine	1.01 ± .05	1.10 ± .04	.274	.88
RSP/UVPM	1.11 ± .04	.44 ± .05	.337	.46
UVPM/FPM	.17 ± .02	.92 ± .02	.140	.96
UVPM/Scopoletin > 1	.67 ± .07	.67 ± .06	.247	.73
UVPM/Scopoletin < 1	0.45 ± .11	.26 ± .12	.388	.10
UVPM/Solanesol	1.74 ± .04	.65 ± .04	.211	.84

ETS = environmental tobacco smoke, UVPM = ultraviolet-absorbing particulate matter, RSP = respirable particulate matter, 3-EP = 3-ethenyl pyridine, FPM = fluorescing particulate matter.

Thus, workplace nicotine concentrations appear to be reasonably well predicted (i.e., within an order of magnitude) by workplace UVPM concentrations in cells 1 and 3 of the 16-City Study.

3.2. Nicotine/RSP

It was anticipated that nicotine would be poorly predicted by RSP, because a wide array of sources besides ETS contribute to total RSP. The regression analysis described previously was used to test this hypothesis. The best-fitting linear model relating $Y = \log_{10}(\text{nicotine})$ to $X = \log_{10}(\text{RSP})$ resulted in the parameters indicated in Table I. It is clear from the low R^2 value (.25) and from Fig. 2 that the fit is poor as indicated by the wide scatter of the points. We therefore conclude that nicotine and RSP are poor predictors of one another.

3.3. Nicotine/3-EP

A plot of $Y = \log_{10}(\text{nicotine})$ versus $X = \log_{10}(3\text{-EP})$ is given in Fig. 3, with the linear model parameters shown in Table I. The R^2 value of .83 indicates a good fit. The quadratic model has a statistically significant quadratic term, but the resulting fit was nearly the same in the range of practical interest (Fig. 3). Because β is very close to 1, nicotine and 3-EP essentially were related linearly with the nicotine concentration equivalent to $10^{0.27}$ (or 1.86) × 3-EP concentration.

Therefore, contrary to what might be anticipated on the basis of differences in the decay rate, 3-EP and nicotine were closely correlated using data from cells 1 and 3 of the 16-City Study and could be used as surrogates for one another. It can further be concluded that 3-EP is likely to be a reasonable marker for UVPM because nicotine and UVPM were related (Section 3.1).

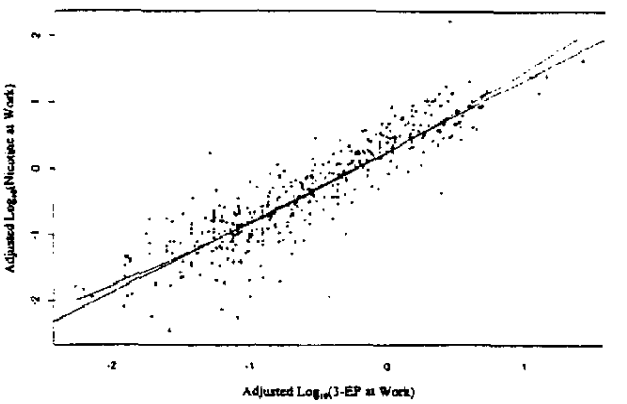

Fig. 3. Scatter plot of $\log_{10}$(nicotine at work) and $\log_{10}$(3-EP at work) (both adjusted for city) with linear and quadratic models.

3.4. Nicotine/Myosmine

Figure 4 presents a plot of $Y = \log_{10}(\text{nicotine})$ vs. $X = \log_{10}(\text{myosmine})$. For this ETS constituent pair, the R^2 value of .88 indicates an extremely good fit (Table I). As was the situation for nicotine and 3-EP, the quadratic fit here had a significant nonzero term, but the fitted quadratic function was nearly identical to the fitted linear function in the practical range of myosmine values. Again, β is close to 1, so

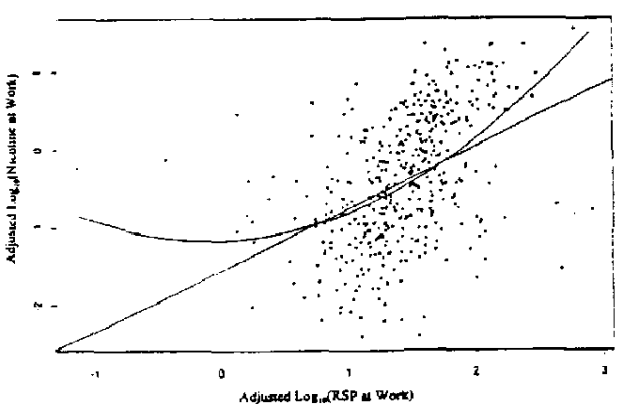

Fig. 2. Scatter plot of $\log_{10}$(nicotine at work) and $\log_{10}$(RSP at work) (both adjusted for city) with linear and quadratic models.

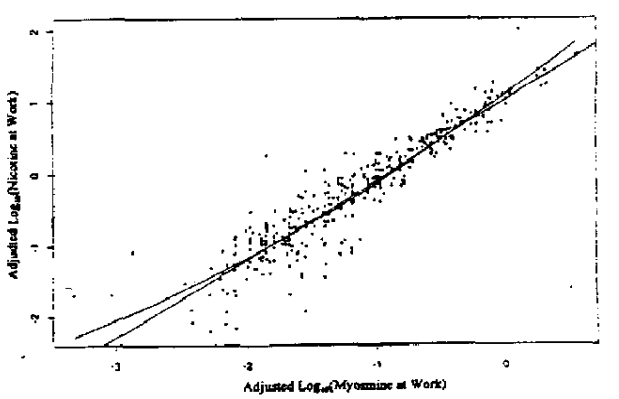

Fig. 4. Scatter plot of $\log_{10}$(nicotine at work) and $\log_{10}$(myosmine at work) (both adjusted for city) with linear and quadratic models.

nicotine and myosmine were linearly related with the nicotine concentration equivalent to $10^{1.01}$ (or 10.2) × myosmine concentration. Therefore, myosmine was a reasonable marker for nicotine and, by extension, UVPM.

3.5. RSP/UVPM

Given that nicotine and UVPM are related (Section 3.1) but that nicotine and RSP are not (Section 3.2), one would predict that UVPM and RSP may not be good predictors of each other, even though both are measures of particulate matter. A plot of $Y = \log_{10}(RSP)$ vs. $X = \log_{10}(UVPM)$ is given in Fig. 5 (parameter values given in Table I). Although the relationship between the two variables is better than that between nicotine and RSP (Fig. 2), the noise is substantial. The quadratic term is significant, and in the region where the quadratic and the linear models differ (i.e., for high and low values of UVPM), the linear model underpredicts the RSP as a function of UVPM. The β regression coefficient is too far from 1 to conclude that RSP and UVPM are linearly related (i.e., the hypothesis that one of the constituents is a fixed fraction of the other is not supported).

3.6. UVPM/FPM

The relationship between these two particulate matter measures related to combustion is of interest.

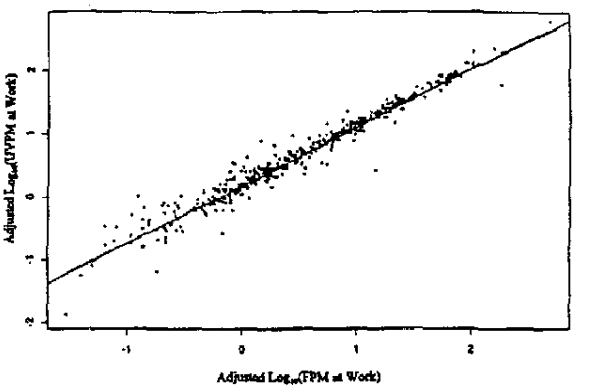

Fig. 6. Scatter plot of $\log_{10}$(UVPM at work) and $\log_{10}$(FPM at work) (both adjusted for city) with linear and quadratic models.

As illustrated in Fig. 6 (and by the parameters given in Table I), the relationship between UVPM and FPM is extremely strong. The quadratic term in the quadratic regression model is not statistically significant. Because β is close to 1, we conclude that there is nearly a linear relation between UVPM and FPM, with UVPM = $10^{0.17}$ (or 1.48) × FPM, so that UVPM was typically 50% higher than FPM. Thus, FPM is a good predictor of UVPM and vice versa.

3.7. Scopoletin/UVPM

From Fig. 7, it is clear that there is a dramatic difference in the UVPM/scopoletin relationship between the range $\log_{10}$(scopoletin) < 0 (i.e., scopoletin < 1) and the range $\log_{10}$(scopoletin) > 0 (i.e., scopoletin > 1). We note that scatter in the lower range

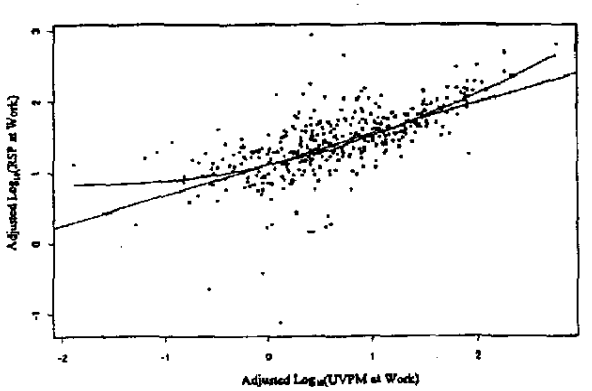

Fig. 5. Scatter plot of $\log_{10}$(RSP at work) and $\log_{10}$(UVPM at work) (both adjusted for city) with linear and quadratic models.

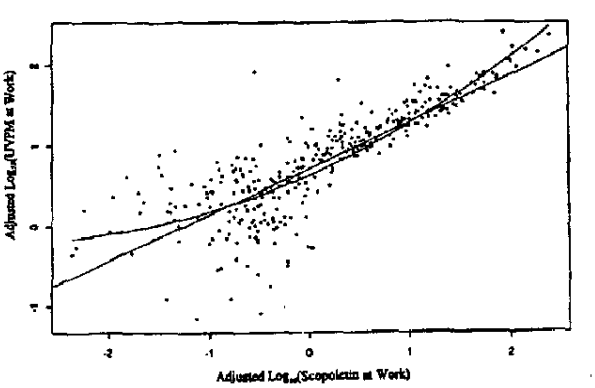

Fig. 7. Scatter plot of $\log_{10}$(UVPM at work) and $\log_{10}$(scopoletin at work) (both adjusted for city) with linear and quadratic models.

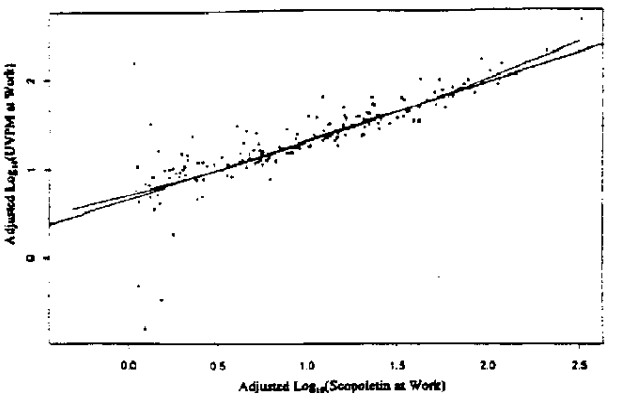

Fig. 8. Scatter plot of $\log_{10}$(UVPM at work) and $\log_{10}$(scopoletin at work) (both adjusted for city) for $\log_{10}$(scopoletin) > 0 (i.e., for scopoletin > 1).

of scopoletin concentrations is scatter at and around the detection limit, and we fit a linear model in each range. (Relevant parameters are provided in Table I.) Because the differences between the regression coefficients are significant, we conclude that log(UVPM) and log(scopoletin) are not linearly related across the entire range of scopoletin concentrations. The linear fit in the upper scopoletin range (Fig. 8) is good ($R^2 = 0.73$). However, in the lower range (Fig. 9), we see virtually no relationship between the two variables ($R^2 = 0.10$). Even if the linear model obtained in the upper scopoletin range is adopted, the β coefficient is far from 1, so we cannot conclude that there is a linear relationship between scopoletin and UVPM in this range. Therefore, on the basis of these data from cells 1 and 3 of the 16-City Study, scopoletin does not appear to be a reliable predictor of UVPM, partly because of the noise around the limit of detection for scopoletin.

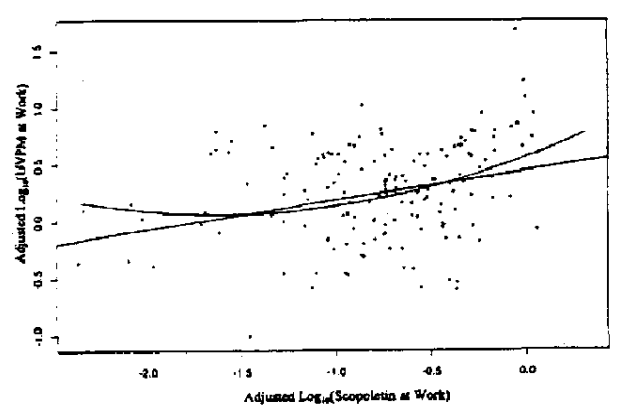

Fig. 9. Scatter plot of $\log_{10}$(UVPM at work) and $\log_{10}$(scopoletin at work) (both adjusted for city) for $\log_{10}$(scopoletin) < 0 (i.e., for scopoletin < 1).

3.8. Solanesol/UVPM

As seen in Fig. 10 and the $R^2 = 0.84$, there is a fairly strong linear relationship between $\log_{10}$(UVPM) and $\log_{10}$(solanesol) (parameter values in Table I). However, the corresponding relationship between untransformed solanesol and UVPM is clearly nonlinear (i.e., β is not close to 1), so it would not be reasonable to assume a constant ratio between these ETS constituents.

McAughey *et al.*[29] found solanesol levels to be approximately 1.3% of total particulate levels (measured as UVPM). Because many sources in the 16-City Study were likely to have contributed to overall UVPM levels, we expected this ratio to be lower than that found by McAughey *et al.* In fact, in the data from cells 1 and 3 of the 16-City Study, the average of the solanesol/UVPM ratios show solanesol to be approximately 0.6% of UVPM, or half the results from McAughey *et al.*

4. RELATIONSHIP BETWEEN EXPOSURE TO ETS AND SALIVA COTININE LEVELS

Another type of marker used to assess ETS exposure is cotinine, a metabolite of nicotine. Because cotinine has been detected in several body fluids, the 16-City Study analyzed for it in saliva.[2,3] Past research on the correlation of saliva cotinine levels

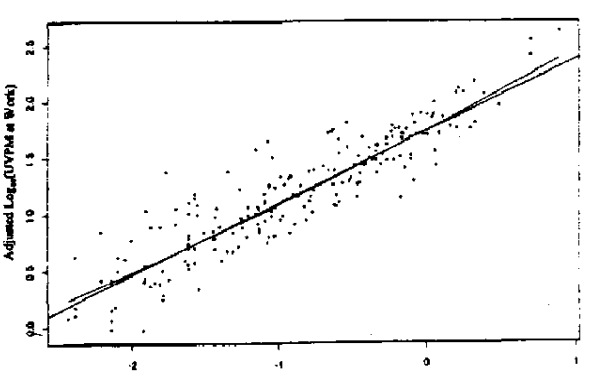

Fig. 10. Scatter plot of $\log_{10}$(UVPM at work) and $\log_{10}$(solanesol at work) (both adjusted for city) with linear and quadratic models.

with self-reported smoking status provides a yardstick for determining the smoking status of study participants. Researchers use saliva cotinine levels as a means for evaluating the reliability of self-reported smoking status. For example, Jarvis and Russell[30] reported that cotinine levels varied systematically with exposure to ETS.

A proposed scale for evaluating the smoking classification of individuals on the basis of saliva cotinine measurements is shown in Table II.[31] Others have reported alternative levels of saliva cotinine as appropriate cutoff points for distinguishing smokers from nonsmokers. For example, a saliva cotinine level of 20 ng/mL was used as the cutoff between smokers and nonsmokers by Jarvis and Russell[30] and Coultas *et al.*[32] Phillips *et al.*[33] conducted a 24-hour personal monitoring study to assess 190 nonsmokers in Stockholm and used 25 ng/mL of saliva cotinine as the cutoff point. In a nationwide study on smoking incidence and misclassification, Ogden *et al.*[34] found the mean saliva cotinine level for self-reported smokers to be 352.9 ng/mL. The authors noted that 10 ng/mL was the "generally recognized concentration level for maximum sensitivity and specificity in delineating current smokers from nonsmokers."

Because of the overlap in saliva cotinine values between high levels of passive smoking and low levels of active smoking, Di Giusto and Eckhard[35] concluded that low-level smokers and those exposed to high levels of passive smoke may be indistinguishable from each other using saliva cotinine as a marker. Indeed, in a large national study of serum cotinine levels (Third National Health and Nutritional Examination Survey, or NHANES III), Pirkle *et al.*[36] reported significant overlap between distributions of participants reporting exposure to ETS and those who were active smokers. In addition, an even greater overlap existed between distributions of persons claiming exposure to ETS and those reporting no exposure, especially at the serum level of 1 ng/mL and below. This suggests that at these very low levels, dietary and other influences may contribute to the body burden of nicotine and its metabolite cotinine.

The inability of researchers to point to a definitive cutoff point for saliva cotinine levels associated with active smoking results from a variety of individually varying factors such as age, smoking status, variation in metabolism and health, and exposure time. These factors are discussed in the following sections.

Table II. Smoking Classification Based on Saliva Cotinine Levels

Saliva cotinine level	Smoking classification
<5 ng/mL	Passive smoking
≥10 ng/mL	Heavy passive smoking
10–100 ng/mL	Infrequent to regular smoking with low nicotine intake
>100 ng/mL	Regular active smoking

Source: Etzel, R. A. "A Review of the Use of Saliva as a Marker of Tobacco Smoke Exposure." *Prevent. Med.* 19(2), p. 195 (1990).

4.1. Age

This variable may be an important individual characteristic that contributes to the wide intersubject variability of cotinine levels.[37] For example, Schievelbein[38] reported less cotinine excretion by older than by younger smokers, possibly because of an age dependancy for nicotine detoxification.

4.2. Smoking Status

There is an inherent difficulty in interpreting the relative cotinine levels in nonsmokers as compared with smokers because of the reported slower nicotine and cotinine metabolism and clearance of cotinine in nonsmokers as well as the lack of good uptake and clearance data for nonsmokers of different ages, sexes, and genetic backgrounds.[39–42]

4.3. Variations in Metabolism

The metabolic rate of nicotine breakdown is affected by intersubject variability arising from physiological, environmental, pathological, and genetic differences.[43] In addition, the half-life of nicotine in the body is approximately 2 hours,[10,44–46] and the half-life of cotinine is 15 to 40 hours.[47] Due to these differences, the correlations between urinary cotinine and reported exposure to ETS vary widely.[48] To reliably use body fluid levels of cotinine as a quantitative estimate of nicotine exposure, one needs information on the extent of interindividual variation in the renal and hepatic clearances of nicotine and cotinine.[18]

4.4. Health and Habits of the Individual

General health status and lifestyle habits such as alcohol consumption influence the ability of the liver to metabolize nicotine.[49]

4.5. Exposure Time

For high nicotine exposures, the detectability of cotinine in blood or saliva is critically dependent on the duration of exposure. According to Balter *et al.*,[118] single time-point samples of blood or saliva are not appropriate as a basis for providing a quantitative estimate of exposure without an understanding of exposure duration. In addition, saliva cotinine is not a sensitive measure for quantifying short-term ETS exposures. A study with nicotine levels from ETS as high as 250 $\mu g/m^3$ did not produce significant changes in saliva cotinine above baseline.[50]

In summary, variability in cotinine data indicates that the usefulness of nicotine and cotinine as quantitative markers for ETS exposure is limited for individuals.[51,52] However, because the sensitivity, specificity, and predictive volumes of saliva cotinine are similar to those of serum cotinine, and because cotinine concentrations in saliva are independent of saliva flow rate, saliva cotinine levels would appear to be useful qualitative indicators of current smoking status for individuals[53] or as a more quantitative marker for larger groups of people.[52]

5. SALIVA COTININE DATA FROM THE 16-CITY STUDY

Saliva cotinine data and nicotine air concentration data from all participants in the 16-City Study[42,3] were analyzed to determine whether these data corroborate the results of the research described in the preceding discussion. Two measurements of saliva cotinine were performed on each participant in the 16-City Study. The first was taken in the evening (9 p.m.) before the 24-hour measurement period began, the second in the late afternoon (4–7 p.m.) after the 24-hour measurement period ended. Thus, there was approximately a one-half day lag between the initial cotinine measurement and the beginning of the workday personal monitoring, and a one-half day delay between the end of the 16-hour away-from-work personal monitoring and the second cotinine determination. This means that the workplace exposure for most study participants ended 24 hours before the second cotinine measurement was collected. Because the half-life of cotinine in the body ranges from 15 to 40 hours,[47] the 24-hour lag between workplace exposure determination and cotinine measurement means that a substantial fraction of the cotinine resulting from the measured workplace exposure may have been excreted already by the time the final cotinine sample was collected in the 16-City Study.

In general, the levels of cotinine found in the saliva of study participants were very low. Only 304 participants in the entire study had average cotinine

Table III. Spearman Correlations Between Beginning and Ending Cotinine Samples and Pearson Correlations Between Log_{10}(Beginning Cotinine) and Log_{10}(Ending Cotinine)

	Cell 1	Cell 2	Cell 3	Cell 4
Spearman[a]	.897	.870	.700	.628
Pearson[b]	.923	.838	.801	.783

[a] Spearman rank correlation coefficient.
[b] Pearson product–moment correlation.

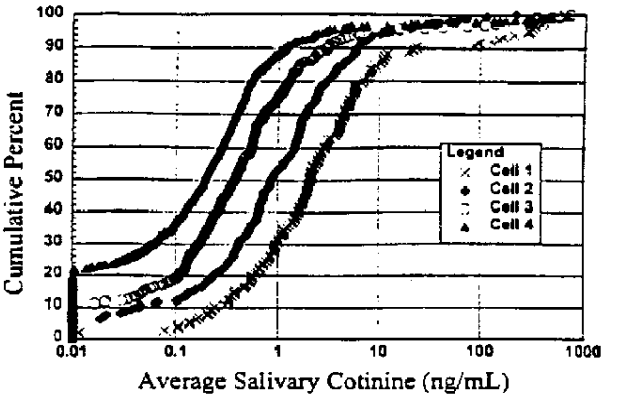

Fig. 11. Cumulative percentage distribution of the average of the beginning and ending saliva cotinine levels for all study participants.

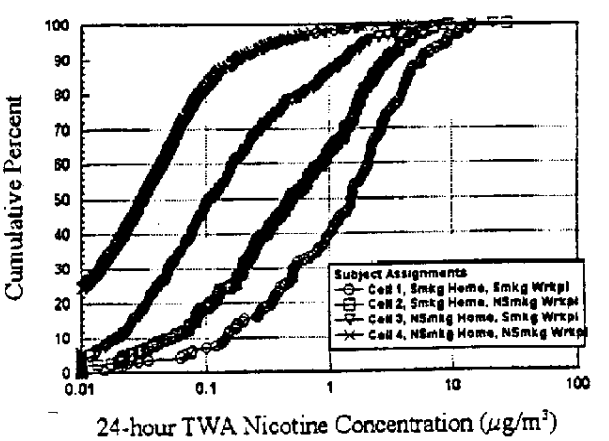

Fig. 12. Cumulative percentage distribution of the 24-hour workplace nicotine time-weighted average (TWA) concentration for all study participants.

Table IV. Comparison of Saliva Cotinine Levels and 24-hour TWA Nicotine Levels Among Cells for Participants Whose Average Cotinine Was Less Than 15 ng/mL (i.e., for Nonsmokers)

Cell	Home environment	Work environment	No. of participants	Median cotinine (ng/mL)[12]	Median 24-h TWA nicotine ($\mu g\ m^{-3}$)
1	Smoking	Smoking	133	1.78	1.55
2	Smoking	Nonsmoking	213	.807	.49
3	Nonsmoking	Smoking	266	.347	.11
4	Nonsmoking	Nonsmoking	790	.182	.03

levels (mean of start and ending samples) greater than the one-sided 95th percentile confidence level (1.01 ng/mL) above the mean limit of detection.

Correlations between initial and final saliva cotinine measurements are shown in Table III. In all cases, the correlations are quite high, ranging from .923 (Pearson product–moment correlation) for cell 1 to .628 (Spearman rank correlation coefficient) for cell 4. Because these were repeated measurements on the same individual, the high correlations were perhaps to be expected. Moreover, the pattern of the correlations is reasonable. That is, the highest intraindividual association was shown by the individuals in cell 1, who were exposed to higher levels of nicotine in both the work and away-from-work environments, whereas the lowest association was shown in cell 4, whose participants experienced only incidental exposure to ETS both at home and at work. It is also worth noting that when one ignores cells and calculates an overall correlation, the Pearson correlation rises to .923, whereas the Spearman correlation is only .742. This reflects the tendency of the Pearson statistic to be inflated by multimodal data to a greater extent than the rank-based Spearman procedure.

The fairly high correlation between the two cotinine measurements taken 2 days apart is also suggestive of saliva cotinine's use as an exposure marker. That is, the data show that cotinine levels were consistent in individuals across a short time period. However, this association should be viewed with caution. We have no data to assess how this association might hold up over a longer period of time. Also, although cotinine levels were consistent for individuals, we do not know if this consistency accurately reflects ETS exposure. That is, a person who rapidly excretes cotinine may show up as having lower exposure than a person who excretes cotinine slowly, even if their exposures were identical.

Considering cotinine on a group rather than an individual level presents a different picture. The distributions of measured cotinine concentrations for the four cells in the study are shown in Fig. 11. In this figure, all participants have been included in the distributions, including those whose saliva cotinine levels clearly indicate that they were at least occasional smokers. This inclusion has the effect of extending the distributions to saliva cotinine levels exceeding 1,000 ng/mL. Cotinine concentrations across the four cells were similar in both level and pattern. Cell 1 had the highest median cotinine level, followed in order by cells 2, 3, and 4. The distribution of nicotine is illustrated in the same way in Fig. 12. A comparison of Figs. 11 and 12 shows that the pattern of distribution for four study cells is similar for nicotine and cotinine.

These data are tabulated in Table IV for those participants whose average saliva cotinine level was below 15 ng/mL, one smoker/nonsmoker discrimination level.[11] For relatively large groups such as this, the correlation between average saliva cotinine (the average of the beginning and ending cotinine samples) and median 24-hour time-weighted average (TWA) nicotine levels was very high ($R^2 = 0.99$ for the numbers in Table IV).

On a group basis, nicotine and cotinine are highly correlated (Table IV) and distinctly different for the study cells (Fig. 11 and 12). The results are different on a individual basis. Figure 13 is a scatter plot of logarithms (base 10) of workplace nicotine air concentrations and average saliva cotinine concentrations, both adjusted for city for the people in cells 1 and 3. As can be seen from the Fig. 13, on an individual basis, there was only minimal correlation between these two indicators of exposure.

Because the levels of both cotinine and nicotine exposure were low, the number of study participants

[11] The cell assignments here were based on self-reported assessment of work and home smoking status.

[12] Median of average cotinine values (i.e., the average of the beginning and ending cotinine samples).

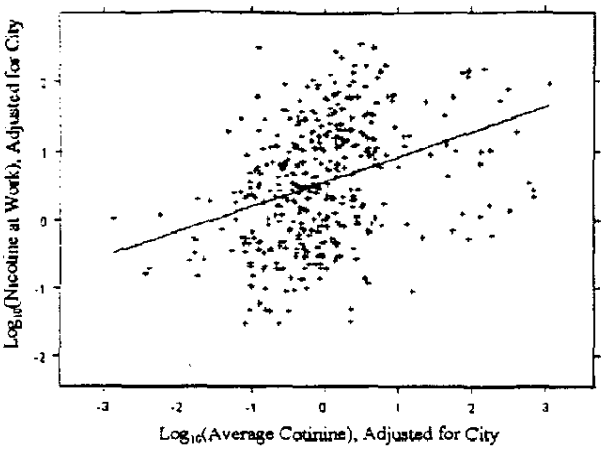

Fig. 13. Scatter plot of $\log_{10}$(nicotine at work) and $\log_{10}$(average cotinine at work) (both adjusted for city) with linear model relating the log-transformed concentrations.

whose saliva cotinine *and* 24-hour TWA level of nicotine exposure were sufficiently high for confident comparison was not large—only 263.[13] Table V presents correlations between various cotinine measures and 24-hour TWA nicotine for those participants whose nicotine and saliva cotinine levels both were greater than the one-tailed 95th percentile confidence level above the mean limit of detection for each of the constituents. All of the correlations were statistically significant at the $p = 0.05$ level except that for change in cotinine between the beginning and ending samples. However, although statistically significant, the correlations are sufficiently small for their biological significance to be questionable. The conclusions from Table V and Fig. 13 are that the use for quantitatively estimated levels of ETS exposure (as measured by personally monitored nicotine concentrations) based on saliva cotinine for individuals is quite limited. Nevertheless, these results suggest that cotinine may have some value as a predictor of chronic exposure to ETS for larger groups of people.

Figure 11 shows that cotinine levels were higher in cell 2 (smoking home, nonsmoking work) than in cell 3 (smoking work, nonsmoking home), suggesting that home exposure may be generally more influential than work exposure in determining total ETS exposure. This postulate is supported by the analysis in Table VI of two subgroups in the study. In Table VI, participants who received all of their ETS exposure outside the workplace are compared with those participants whose only ETS exposure was in the workplace. The first group (those exposed away from work) reported no exposure in the workplace (they worked in a nonsmoking workplace and reported no tobacco products being used around them at work) and received most of their ETS exposure from living with a spouse who smoked anywhere within the home. The second group (those exposed at work) worked in an environment wherein smoking was unrestricted, reported tobacco products being smoked around them in the workplace, and received no exposure outside the workplace (i.e., they lived in nonsmoking homes and reported no tobacco products being smoked around them away from work).

For the group exposed to ETS only at work, the median, mean, and 80th percentile average cotinine levels were less than the one-sided 95th percentile upper confidence limit for the mean level of detection (1.01 ng/mL). In other words, the cotinine measures in this group were very low. The average saliva cotinine levels for the cell 2 participants (all exposure outside of work) were definitely greater than those of the cell 3 participants (exposure only at work). The 24-hour TWA levels of 3-EP and nicotine for people in cell 2 were greater than those for people in cell 3 as well, in approximately the same proportion as the average saliva cotinine levels. The differences were maintained across the range of participants, including those who were most highly exposed (e.g., the 95th percentile). These data provide additional support for the home being a more important source of ETS exposure than the workplace.[23]

Table V. Correlation Between Saliva Cotinine and 24-hour TWA Nicotine Levels for Participants with Both Measures Greater Than the 95th Percentile Confidence Interval Above the Mean Limit of Detection

Regression	Correlation coefficient, R
Beginning cotinine vs. 24-h TWA nicotine	.200
Ending cotinine vs. 24-h TWA nicotine	.327
Average cotinine[14] vs. 24-h TWA nicotine	.324
Δ Cotinine (ending–beginning) vs. 24-h TWA nicotine	.114

TWA = time-weighted average.

[13] Of the 304 participants with sufficient cotinine values, 41 did not have 24-hour TWA nicotine levels greater than the 95th percentile confidence limit above the mean limit of detection.

[14] Mean of beginning and ending cotinine levels.

Table VI. Comparison of ETS Markers (Average Cotinine, 3-EP, and Nicotine 24-hour TWA) Between Study Participants Whose Only Source of ETS Exposure Was Away from Work With Those Whose Only Source of ETS Exposure Was the Workplace

	Participants who received all ETS exposure away from work[15] (N = 39)			Participants who received all ETS exposure at work[16] (N = 44)		
Parameter	Average continine (ng/mL)	3-EP 24-h TWA ($\mu g/m^3$)	Nicotine 24-h TWA ($\mu g/m^3$)	Average cotinine (ng/mL)	3-EP 24-h TWA ($\mu g/m^3$)	Nicotine 24-h TWA ($\mu g/m^3$)
Median	1.47	.72	1.29	.42	.16	.35
Mean	1.94	.81	1.59	.62	.32	.69
80th Percentile	3.05	1.33	2.48	.87	.48	1.38
95th Percentile	5.73	2.22	3.79	2.36	1.22	2.11

ETS = environmental tobacco smoke. TWA = time-weighted average. 3-EP = 3-ethenyl pyridine.

6. DISCUSSION

The ETS workplace data from cells 1 and 3 of the 16-City Study[2] were used to examine selected ETS-related chemicals for their use as markers of exposure to other ETS chemicals in workplaces where smoking is permitted.[17] The results of the analyses suggest that nicotine is a reasonably good (i.e., within one order of magnitude) predictor of UVPM, which is composed of combustion-derived chemicals. The correlation between nicotine and RSP was found to be weak as was anticipated because of the multiple source contributions to RSP concentrations. The use of the gas-phase compounds 3-EP and myosmine as predictors of nicotine (and by extension, UVPM) was supported.

For the particulate-phase relationships, UVPM levels were found to be closely correlated with FPM and approximately 50% higher. Thus, the use of UVPM concentrations to predict ETS exposure would provide more conservative estimates than the use of FPM concentrations. The relation between UVPM and solanesol was good but not linear for the untransformed concentrations. The correlations between RSP and UVPM and between scopoletin and UVPM were not sufficiently strong to indicate that one would be a reliable marker for another.

In conclusion, there was a high degree of correlation between selected pairs of ETS constituents. However, even in the case of substantial correlation between pairs of markers, their use as quantitative predictors of each other (and hence of ETS exposure) is limited, with the exception of the UVPM–FPM pair.

Saliva cotinine clearly is related to exposure of airborne nicotine, but cotinine is useful only as a quantitative predictor for large groups of subjects. Continuing the investigation of the relative impact of work and away-from-work or home exposure begun in the first article of this series, the 16-City Study data point to the home as a more important source of exposure than the workplace.

[15] These participants who received all ETS exposure away from work are from cell 2. They work in places where smoking is not permitted, observed no smoking at work, and have confirmed unrestricted spousal smoking at home.

[16] These participants who received all ETS exposure at work are from cell 3. They work in locations with no restrictions on smoking and confirmed that they observed no smoking in the home or elsewhere away from work.

[17] Overall, concentration levels were lower in the other cells (cells 2 and 4 where smoking was not permitted in the workplace). Hence, the concentration range available for pairwise prediction was not as wide in these cells.

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Data from the 16-City Study used in this series of articles are available on CD-ROM from Carol G. Graves, The Sapphire Group, 3 Bethesda Metro Center, Suite 700, Bethesda, Maryland 20814. Please include a check for $10 (U.S.) to cover costs.

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